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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/051,159	01/13/1999	Allan Balmain	CCI-005US	7671

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EXAMINER
SCHNIZER, RICHARD A

ART UNIT	PAPER NUMBER
1635	

DATE MAILED: 01/15/2003

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No. 09/051,159	Applicant(s) Balmain
	Examiner Richard Schnizer	Art Unit 1635

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136 (a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1) ☒ Responsive to communication(s) filed on *Oct 15, 2002* .

2a) ☐ This action is **FINAL.** 2b) ☒ This action is non-final.

3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11; 453 O.G. 213.

Disposition of Claims

4) ☒ Claim(s) *1-13 and 15-25* is/are pending in the application.

4a) Of the above, claim(s) _____ is/are withdrawn from consideration.

5) ☐ Claim(s) _____ is/are allowed.

6) ☒ Claim(s) *1, 4, 8, 15, 16, and 20-25* is/are rejected.

7) ☒ Claim(s) *2, 3, 5-7, 9-13, and 17-19* is/are objected to.

8) ☐ Claims _____ are subject to restriction and/or election requirement.

Application Papers

9) ☐ The specification is objected to by the Examiner.

10) ☒ The drawing(s) filed on *Jan 13, 1998* is/are a) ☒ accepted or b) ☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11) ☐ The proposed drawing correction filed on _____ is: a) ☐ approved b) ☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12) ☒ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13) ☒ Acknowledgement is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a) ☒ All b) ☐ Some* c) ☐ None of:

1. ☐ Certified copies of the priority documents have been received.
2. ☐ Certified copies of the priority documents have been received in Application No. _____ .
3. ☒ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

*See the attached detailed Office action for a list of the certified copies not received.

14) ☐ Acknowledgement is made of a claim for domestic priority under 35 U.S.C. § 119(e).

a) ☐ The translation of the foreign language provisional application has been received.

15) ☐ Acknowledgement is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449) Paper No(s). _____
4) ☐ Interview Summary (PTO-413) Paper No(s). _____
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other:

DETAILED ACTION

Continued Examination Under 37 CFR 1.114

1. A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on 10/15/02 has been entered.

Applicant's amendment filed 10/15/02 was entered as Paper No. 24.

Claim 14 was canceled and claim 25 was added as requested.

Claims 1-13, and 15-25 are pending and under consideration in this Office Action.

The Examiner and Art Unit associated with this application have changed. Please direct further correspondence to Richard Schnizer, Art Unit 1635.

Oath/Declaration

2, The original Declaration for Patent Application was objected to in Paper No. 15 because, while it contained the signature of listed inventor Allan Balmain, it lacked the signature of listed inventor Jingde Zhu. Subsequently Applicant submitted a second Declaration for Patent Application which named Jingde Zhu as the original, first, and sole inventor of the instant invention, but which did not list Allan Balmain as an inventor. In a telephone interview conducted

in December of 2002, Cynthia Kanik indicated that Allan Balmain was still intended to be an inventor on the application. For this reason, a supplemental declaration listing all inventors, and signed by Jingde Zhu is required.

Claim Objections

3. Claims 2, 3, 5-7, 9-14, and 17-19 are objected to because they depend from a rejected claim but would be allowable if rewritten as independent claims incorporating all the limitations of the parent claim(s).

Claim Rejections - 35 USC § 101

35 U.S.C. 101 reads as follows:

> Whoever invents or discovers any new and useful process, machine, manufacture, or composition of matter, or any new and useful improvement thereof, may obtain a patent therefor, subject to the conditions and requirements of this title.

4. Claims 1, 4, 8, 15, 16, 20, and 25 rejected under 35 U.S.C. 101 because the claimed invention is directed to non-statutory subject matter because human beings can be considered to be compositions of matter comprising nucleic acids with the characteristic set forth in these claims. For example, humans generally comprise wild type p53 and HSP70 genes comprising p53 and HSP70 promoters. The HSP70 gene corresponds to the first nucleic acid construct of the claims, whereas the p53 gene corresponds to the second nucleic acid construct of the claims. The

specification teaches at page 11, lines 13-17 that p53 is a sequence specific transcriptional suppressor of the HSP70 promoter, as required by claim 4. Claim 8 requires that the genes must be on separate nucleic acid vectors. In humans p53 and HSP70 are located on separate chromosomes (see Le Beau et al (Nature (1985) 316(6031): 826-828, 1985) and Shimuzu et al (Biochim. Biophys. Res. Comm. (1996) 219(3): 745-752)). HSP70 can be considered to be a reporter gene, as required by claim 16, because it is detectable. Finally, the nucleic acids are comprised within cells as required by claim 20.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

5. Claims 22 and 23 stand rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for in vitro methods of introducing nucleic acid constructs encoding an antitumor agent into a cell, and for in vivo methods of introducing such constructs directly into cells of a tumor, does not reasonably provide enablement for in vivo methods of introducing nucleic acid constructs into all cells by any delivery route as broadly claimed. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to use the invention commensurate in scope with these claims.

Nature of the invention

6. The rejected claims are methods of delivering nucleic acid constructs to cells. A review of the specification reveals that the in vivo aspect of the invention is a means of treating tumors by delivering to cells nucleic acids encoding a cytotoxic agent, and limiting to tumor cells the expression of the cytotoxic agent. Briefly, a first promoter is operably linked to a sequence encoding a cytotoxic agent, wherein the promoter is negatively regulated by wild type p53 or $p16^{INK-4}$ in non-tumor cells, but positively regulated by p53 in tumor cells. A second promoter is operably linked to a sequence encoding a negative regulator of the cytotoxic agent, wherein the second promoter is negatively regulated in tumor cells, but positively regulated in non-tumor cells. These two expression constructs may be present on a single nucleic acid, or may be delivered on separate nucleic acids. Presence of both constructs in a tumor cell results in expression of the cytotoxic agent. The construct comprising the cytotoxic agent should not be well-expressed in non-tumor cells, and should function even more poorly in non-tumor cells comprising the second construct.

Breadth of the claims

7. The specification asserts no in vivo purpose for the claimed methods other than the therapeutic treatment of tumors. For example, the specification does not present any practical utility or provide sufficient guidance for using the compositions or methods comprising anything other than a pro-drug activating enzyme (i.e. TK) in the of the first nucleic acid construct to kill tumor cells in a body. Neither the claims nor the specification limits the types of tumors that

could be treated using the claimed methods. The claims do not limit the route of administration of the expression constructs, nor the nature of the delivery vector, e.g. all viral and nonviral delivery means, as well as systemic delivery routes, are implicitly embraced.

State of the prior art, unpredictability of the art, and level of skill in the art.

8. At the time of filing, the relevant art considered gene therapy as a whole to be unpredictable as modes of delivery that would provide efficient delivery and expression of genes encoding the therapeutic protein sufficient to provide an alleviation of symptoms related to the target disease or condition had not been developed. This is not to say that gene delivery and expression at a sub-therapeutic level was unpredictable at the time of filing. Blau et al stated that the main challenge in gene therapy is the achievement of efficient vector delivery and gene expression (Blau et al (1995), page 1204, col. 1-2 bridg. Sent: and page 1205, col. 1-2 bridg. Sent.). Crystal (1995) stated that human gene transfer still faces significant hurdles before it becomes an established therapeutic strategy (abstract) and that the human transfers had been plagued with inconsistent results (page 409, col. 1, parag. 2, lines 1-4). Miller et al (1995) that before gene therapy is an option for treating genetic diseases, there is a requirement to produce vector systems that can deliver therapeutic genes to the appropriate target cells either in vivo or ex vivo accurately and efficiently (page 190, col. 1, parag. 1, lines 1-7).

9. Orkin et al. reviewed the infant state of the art of gene therapy at around the time the invention was made. The overall conclusions were: 1) gene therapy for each disease would present its own scientific and clinical challenges; 2) no successful gene therapy protocol was

known; 3) significant problems remained in all aspects of gene therapy, especially with respect to effective expression vectors; 4) the pathophysiology of diseases to be treated were poorly understood; 5) one cannot predictably extrapolate the result of one animal model, such as mouse, to treatment of a disease in a different animal, such as human; 6) assessment of known gene therapy protocols was hindered by poor gene transfer, reliance on qualitative, rather than quantitative assessments of gene transfer, lack of suitable controls and poor definition of biochemical or disease endpoints; and 7) that gene therapy has been oversold, and the impression that gene therapy is successful is mistaken (pages 1-2). The specification does not teach how one skilled in the art is to overcome any of the problems that have plagued gene therapy.

10 Verma et al (1997) states that gene delivery is the "Achilles heel" of gene therapy, and that the ability to deliver and expression genes efficiently to obtain sustained expression is needed for effective therapy (page 239, col. 3, parag. 1.). Ross et al (1996) state that the technical impediment to gene transfer (as a therapy) is the lack of vector systems, and that unless it is possible to deliver the gene to the appropriate blood or body cells and in sufficient quantities, gene therapy will not be efficacious (page 1782, col. 2, parag. 1, lines 1-4). Although the level of technical skill of those who practice the art is high, it must be considered in light of the challenges in the art, which are clearly greater than those of skill were able to routinely surmount at the time of the invention.

11. Because the claims embrace methods of systemic delivery in vivo, this issue must also be addressed. While progress has been made in recent years for *in vivo* gene transfer, vector

targeting *in vivo* to desired sites continues to be unpredictable and inefficient. This is supported by numerous teachings available in the art. For example, Miller et al. reviews the types of vectors available for *in vivo* gene therapy, including retroviral, adenoviral, liposomal, and molecular conjugates, and conclude that "for the long-term success as well as the widespread applicability of human gene therapy, there will have to be advances...targeting strategies outlined in this review, which are currently only at the experimental level, will have to be translated into components of safe and highly efficient delivery systems" (page 198, column 1). Deonarain reviews ligand-targeted receptor mediated vectors, and indicates that one of the biggest problems hampering successful gene therapy is the "ability to target a gene to a significant population of cells and express it at adequate levels for a long enough period of time" (page 53, first paragraph). Deonarain reviews new techniques under experimentation in the art which show promise, but which are currently even less efficient than viral gene delivery (see page 65, first paragraph under Conclusion section). Verma et al. (1997) reviews various vectors known in the art for use in gene therapy and the problems which are associated with each. Verma clearly indicates that at the time of the claimed invention resolution to vector targeting had not been achieved in the art (see entire article). Verma discusses the role of the immune system in inhibiting the efficient targeting of viral vectors such that efficient expression is not achieved (see page 239 and 2nd and 3rd column of page 242. Crystal also reviews various vectors known in the art and indicates that "among the design hurdles for all vectors are the need to increase the efficiency of gene transfer, to increase target specificity and to enable the transferred gene to be regulated" (page 409). While the

specification teaches means to control the specificity of gene expression once a vector has entered a cell, it fails to provide adequate guidance as to how to achieve delivery to specific target cells by systemic administration. The specification fails to teach any specific targeting techniques, fails to provide any working examples which encompass vector targeting, and fails to direct the skilled artisan to any teachings of targeting strategies known in the art which would allow one of skill in the art to practice the claimed invention without undue experimentation.

12. In view of the unpredictability and lack of success in the art at the time of filing, gene therapy can only be considered predictable in being shown not to work. Thus to overcome these teachings in the art the specification would need to supply direct, correlative guidance as to the vector, the promoter, the expression level, the route of delivery and dosage amounts/frequency that are effective in alleviating symptoms of disease using the claimed expression system. Thus, the need for working examples in appropriate animal model studies is critical.

Guidance and exemplification in the specification.

13. Apart from a prophetic example (e.g. p. 59), the specification lacks the appropriate specific guidance referred to above that would be necessary to overcome the problems and the unpredictability in the art. Specifically, there are no teachings in the specification that would provide the artisan with any treatment regime to achieve a therapeutic benefit by in vivo or ex vivo gene therapy and provides no correlation between vectors, cells comprising vectors, routes of delivery (e.g. intratumoral, intravenous etc.), dosage amounts/frequencies, and specific tumors treatable by the said of the instant specification. Such specific teachings are particularly

necessary, since e.g. bystander-mediated killing as proposed in the instant specification (e.g. p. 2) was known at the time of filing as being dependent on the extent of heterocellular communication mediated by gap junctions (Fick et al., Proc. Natl. Acad. Sci. USA, 92:11071-11075, 11/95) whose effects are variable among different tumor cells (Beck et al., Hum. Gene Ther., 6:1525-1530, 12/95). Specifically, the specification provides no guidance concerning the specific types of tumors amenable to the bystander effect in accordance with the claimed invention, including routes of vector administration, ganciclovir dosages etc. For example, even though administration of a single vector comprising both nucleic acid constructs would be much more efficient for co-delivery of nucleic acid constructs compared to *co*-transfection (or administration) of two independent nucleic acid constructs, the specification does not disclose what amounts of vector and prodrug need to administered or co-administered (in either case) so as to allow sufficient discrimination between tumor and non-tumor cells to result in e.g. selective TK expression in tumor cells to produce a therapeutic benefit.

14. To enable the instantly claimed embodiments directed to gene therapy, the specification must provide the critical mass of novel aspects of the invention for the successful practice of gene therapy. Although the p53-pathway-directed vector compositions of the instant application provide one sub-embodiment that would be useful in principle for ***developing*** a gene therapy against certain types of cancers, the novel features for enabling such cancer gene therapy must ***additionally*** address e.g. the problems and unpredictability in the art as directed to targeting and

achievement of efficacious transgene levels in vivo comprising sufficiently novel aspects in a methodological sense to overcome the problems in the art.

Amount of experimentation required

15. Absent sufficient *specific* guidance for the novel aspects which enable *in vivo* targeting, delivery, and selective tumor-specific expression of e.g. cytotoxins providing a therapeutic benefit, such that the approach overcomes the problems and lack of success in the art at the time of filing, it would require undue experimentation to enable the scope of the claimed compositions and methods recited in claims 22 and 23. Amending the claims to be directed at isolated cells or in vitro methods would obviate this particular basis for the rejection (in addition to reciting specific enabled embodiments in said claims).

Response to Arguments

16. Applicant's arguments filed 10/15/02 have been fully considered as they apply to the grounds of rejection set forth above, but they are not persuasive.

17. Applicant considers the gene therapy aspects of enablement at pages 6 and 7 of the response.

18. Applicant argues that the utility of the invention is not limited to gene therapy. This is unpersuasive because the scope of the invention found to be non-enabled is precisely that scope that corresponds to gene therapy as broadly claimed.

19. Applicant argues that Lipinski et al (2001) constitutes post-filing evidence of reduction to practice of the claimed invention. This is unpersuasive for the following reasons. Lipinski teaches the use of the claimed invention to treat a tumor model consisting of human colorectal tumor cells (SW480) xenografted subcutaneously into mice. Specifically, an adenoviral vector comprising both constructs was delivered to the site of a tumor, and an increase in survival of the mice was observed. The first consideration in the enablement analysis is whether or not the xenograft model of Lipinski constitutes an adequate animal model of cancer. The state of the art of animal cancer models is relatively unpredictable. This is evidenced by the statement of Alan Oliff, executive director for cancer research at Merck Research Laboratories who said "[t]he fundamental problem in drug discovery for cancer is that the model systems are not predictive at all". See Science 278:1041-1042, 11/7/97, at page 1041, column 1, paragraph 2. Furthermore, although early failures in drug development were blamed on tests being performed the disimilarity of mouse and human tumors, the use of xenografts of human tumors in mice failed to improve the situation. See page 1041, column 2, paragraph 2. It is also worth noting that the prior art teaches that the site of tumor implantation in xenograft models can greatly influence biological properties of the model. Viewig (Cancer Invest. 13(2): 193-201 (1995)) teaches that "appropriate animal models should be based on the choice of a highly relevant animal tumor model that corresponds in its origin and tumor biology with a particular from of human cancer, as well as on orthotopic implantation of the tumor cells into their organ of origin." In this case, the SW480 cells were not implanted into the appropriate orthologous tissue (colon/rectum), but were implanted into a non-

analogous tissue (skin). In view of the teachings of those of skill in the art regarding the relevance of cancer models in general, and non-orthotopic xenografts specifically, the results of Lipinski cannot be seen as enabling of the claims, because the model used in Lipinski does not appear to be an art-accepted animal model of human colorectal cancer. Furthermore, although Lipinski shows that the invention can be used to effect gene expression in vivo when administered by a viral vector systemically, there is no evidence to indicate that sufficient delivery to tumor cells is achieved by this route of administration. Similarly no evidence is presented regarding the enablement of non-viral delivery means embraced by the claims.

The following is a quotation of the second paragraph of 35 U.S.C. 112:

The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

20. Claims 22 and 23 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

21. Claims 22 and 23 are indefinite because they fail to recite any intended outcome of the method, so it is unclear what method/process applicant is intending to encompass.

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless -
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

22. Claims 1, 4, 8, 15, 16, 20, 21, and 25 are rejected under 35 U.S.C. 102(b) as being anticipated by Symonds et al (J. Virol. (1991) 65(10): 5417-5424).

23. Symonds teaches a cell (a composition) comprising wild type p53 gene and an HSP70 gene. Absent evidence to the contrary, these genes comprise a p53 promoter and an HSP70 promoter, respectively. The HSP70 gene corresponds to the first nucleic acid construct of the claims, whereas the p53 gene corresponds to the second nucleic acid construct of the claims. As discussed in the specification. The specification teaches at page 11, lines 13-17 that p53 is a sequence specific transcriptional suppressor of the HSP70 promoter, as required by claim 4. Claim 8 requires that the genes must be on separate nucleic acid vectors. Symonds meets this claim inasmuch as the p53 and HSP70 genes are known to be located on different chromosomes. See e.g. Ohashi et al (Genomics (1995) 30(2): 406-407) who report that mouse HSP70 is on chromosome 18, and Rotter et al (Mol. Cell. Biol. (1984) 4(2):383-385) who report that mouse p53 is on chromosome 11. HSP70 can be considered to be a reporter gene, as required by claim 16, because it is detectable. The cells of Symonds are tumor cells, as required by claim 21.

Thus Symonds anticipates the claims.

24. Claims 1, 4, 8, 12, 16, 20-25 are rejected under 35 U.S.C. 102(b) as being anticipated by Yamaguchi et al (Eur. J. Biochem. (1994) 221: 227-237).

25. Yamaguchi teaches neuroblastoma cell comprising both a plasmid vector encoding the PCNA promoter operably linked to a CAT reporter gene, and a plasmid vector encoding wild type p53 operably linked to a CMV promoter. Yamaguchi also teaches a method of making the cells by delivering both the plasmids to neuroblastoma cells in vitro. See abstract, page 228, column 1, first sentence of first full paragraph, column 2, first sentence of first full paragraph, and column 2, third full paragraph.

Thus Yamaguchi anticipates the claims.

Summary

Claims 1, 4, 8, 15, 16, 20, and 25 are rejected under 35 USC 101.

Claims 22 and 23 stand rejected under 35 USC 112 for lack of enablement and indefiniteness.

Claims 1, 4, 8, 15, 16, and 20-25 are rejected under 35 USC 102(b).

Claims 2, 3, 5-7, 9-13 and 17-19 are objected to because they depend from a rejected claim but would be allowable if rewritten as independent claims incorporating all the limitations of the parent claim(s).

Conclusion

No claim is allowed.

Any inquiry concerning this communication or earlier communications from the examiner(s) should be directed to Richard Schnizer, whose telephone number is 703-306-5441. The examiner can normally be reached Monday through Friday between the hours of 6:20 AM and 3:50 PM. The examiner is off on alternate Fridays, but is sometimes in the office anyway.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, John Leguyader, can be reached at 703-308-0447. The FAX numbers for art unit 1632 are 703-308-4242, and 703-305-3014. Additionally correspondence can be transmitted to the following RIGHTFAX numbers: 703-872-9306 for correspondence before final rejection, and 703-872-9307 for correspondence after final rejection.

Inquiries of a general nature or relating to the status of the application should be directed to the Patent Analyst Trina Turner whose telephone number is 703-305-3413.

Richard Schnizer, Ph.D.

Jeffrey Siew
JEFFREY SIEW
PRIMARY EXAMINER
1/12/03